

REMARKS

1. Amendments to the Claims

Claims 3-5, 13-14, 17-19, and 22 are pending. Claims 3, 4, 14, 17-18, and 22 are herein amended. Support for the amendments to the claims is found at page 8, lines 30-31 of the Specification. New claims 23-25 are added. Support for new claims 23-25 can be found in the Specification at page 8 lines 31-33, page 10, lines 19-21, page 19, lines 32-34, and page 28, beginning at line 13. No new matter has been added.

2. Rejection Under 35 U.S.C. § 112

The Examiner rejects claims 3-5, 13-14, 17-18, and 22 under 35 U.S.C. § 112, second paragraph as being indefinite. The Examiner rejects claims 3-4, 14, and 18 for the recitation of 75% benzyl ester of hyaluronic acid, stating that it is not clear what the rest of the 25% constitutes. (Office Action, pages 2-3).

Claims 3, 4, 14, and 18, have been amended to define the other 25% of carboxylic acid groups. Claims 5, 13, and 17 are dependant from the amended claims. Applicants submit that the claims define the other 25% of carboxylic acid groups and are therefore clear. Applicants request that the Examiner withdraw the rejection.

3. Rejection Under 35 U.S.C. § 102(e)

The Examiner rejects claim 4 under 35 U.S.C. §102(e) as being anticipated by Valentini (U.S. 5,939,323). Applicants respectfully traverse.

The Examiner asserts that a 75% benzyl ester of hyaluronic acid is taught at col. 9, lines 39-40. Applicants note that the form taught by Valentini describes the generation of a paste of hyaluronic acid which is combined with a NaCl crystals. (Valentini, col. 9, lines 44-50). However, Applicants submit that the scaffolds of Valentini are not in the form of a non-woven fabric, as recited in claim 4. Specifically, Valentini describes **foams** or sponges. (See, e.g.,

Valentini, col. 9, line 56 “water treatment is stopped when the foams have floated and expanded slightly”).

Accordingly, Applicants submit that Valentini fails to teach every element of claim 4. Applicants request that the rejection be withdrawn.

4. Rejection Under 35 U.S.C. § 103

The Examiner rejects claims 3, 5, 13-14, 17-19, and 22 under 35 U.S.C. § 103 as being unpatentable over Davidson in view of Valentini (U.S. 5,939,323).

Davidson and Valentini

a. The combination of Davidson and Valentini would not give one of skill any reasonable expectation that the claimed methods would be effective.

Applicants reiterate that the Davidson reference refers to the ethyl ester of hyaluronic acid. (Davidson, page 172, col. 1, lines 10, and 43-44). Based on the Davidson reference itself, hyaluronic acid and hyaluronic acid 75% ethyl ester did not show any significant improvement in the progression of wound healing. (Davidson, page 174, col. 1, lines 3-6 and 25-28, discussed in the Zanellato Declaration dated April 14, 2008, page 3). Furthermore, Applicants have presented evidence demonstrating that in a direct comparison, the ethyl ester had > 40% more scarring (scarred areas of treatment) than treatment with a benzyl ester. (Zanellato Declaration, dated February 3, 2009, page 2, point 8). More importantly, scarring was increased in animals treated with the ethyl ester of hyaluronic acid as compared to controls. (Zanellato Declaration, February 3, 2009, page 2). Thus, based on Davidson one of skill in the art would have **no reasonable expectation** that 1) hyaluronic acid (and its derivatives) would work better than controls at wound healing or reducing scarring, and 2) the benzyl ester of hyaluronic acid (as opposed to the ethyl ester) would be significantly better than either the ethyl ester *or* controls at improving wound healing and reducing scarring.

Adding Valentini to Davidson does not remedy these deficiencies. Valentini discloses the use of a hyaluronic acid scaffold or foam for “tissue repair, tissue reconstruction and wound healing.”

(Valentini, abstract). Based on Davidson, which tested both hyaluronic acid and the ethyl ester of hyaluronic acid, neither showed any improvement over treatment with the vehicle (alginate). Simply because Valentini proposes the use of both the total benzyl ester of hyaluronic acid and the 75% benzyl ester of hyaluronic acid in a different form and for a different purpose would not lead one of skill in the art to expect that 1) the benzyl ester would work for the reduction of scarring, or 2) the 75% benzyl ester would be significantly better than the total benzyl ester at the reduction of scarring than the total benzyl ester.

b. Additional evidence and statements from one of skill in the art demonstrate that the presently claimed methods show unexpectedly improved reduction in scarring.

Even further, Applicants herein provide a Declaration from Dr. Callegaro which provides evidence showing the efficacy of a non-woven fabric of HYAFF 11p75 (*i.e.*, the 75% benzyl ester) to the treatment with a laser skin autograph which is comprised of a 100% benzyl ester of hyaluronic acid, and a combination of treatment with both the 75% benzyl ester and the total benzyl ester of hyaluronic acid.

In the Declaration, Dr. Callegaro indicates that the 75% benzyl ester of hyaluronic acid performs better than the total benzyl ester of hyaluronic acid. (Callegaro Declaration, page 3) In addition, the 75% benzyl ester provided “a better organized wound bed” and a strong angiogenic response (*i.e.*, directed angiogenesis). (Callegaro Declaration, page 4).¹ Also, Dr. Callegaro states that the addition of the 100% benzyl ester to the treatment with the 75% benzyl ester did not seem to significantly increase wound healing. (Callegaro Declaration, page 4).

Furthermore, Dr. Callegaro indicates that one of skill in the art would expect that the total benzyl ester would be the best material for tissue implant/repair and wound healing because Campoccia (Biomaterials 19 (1998) 2101-2127) indicates that the partial benzyl ester of hyaluronic acid (HYAFF 11p75) produces side effects regarding cell proliferation, adhesion and cell inflammation. (Callegaro Declaration, page 4). Thus, in his *opinion* as one of skill in the art, supported by the evidence in the Navsaria Report, a skilled practitioner would be led to use the

¹ Moreover, the relatively fast degradation of the 75% benzyl ester of hyaluronic acid when compared to the total benzyl ester may account for the angiogenic effects based on the increased ability of the 75% benzyl ester to produce fragments of hyaluronic acid oligomers.

total benzyl ester of hyaluronic acid, and therefore the benefits obtained with the 75% benzyl ester would be unexpected.

Thus, Applicants submit that this additional evidence supports that one of skill in the art would have no reasonable expectation of success in using the partial benzyl ester in the claimed methods.

Furthermore, Applicants submit that the evidence presented by Dr. Callegaro also supports the unexpectedness of the results obtained with the 75% benzyl ester of hyaluronic acid in a wound-healing and scarring model *in vivo*.

c. The Examiner's reference to the instant Specification to establish that one of skill in the art would have a reasonable expectation of success is improper.

The Examiner refers to instant Specification to establish that the expectation of success is "reasonable". The Examiner states:

Since the instant specification provides experimentation of scarring treatment after creating [a] wound in an animal and then observing the scarring effect, it is evident that wound healing ester of hyaluronic acid of Valentini would treat scarring as per Davidson et al absent evidence to the contrary. (Office Action, page 5).

Applicants submit that the Examiner's reliance on the present application to provide the "reasonable expectation of success" based on the combined references is wholly improper, and smacks of hindsight reasoning. *See e.g., In re Omeprazole Patent Litigation*, 82 U.S.P.Q.2d 1643, 1656 (Fed. Cir. 2007).

Applicants have demonstrated through multiple Declarations that one of skill in the art would have expected the total benzyl ester of hyaluronic acid to be better at wound healing with decreased scar tissue. As described in Zanellato Declaration 2 (filed on March 9, 2009) a non-woven fabric of the 75% benzyl ester of hyaluronic acid provides superior characteristics to the total benzyl ester. There is no reason in either Valentini or Davidson to choose one over the other, and in fact in the Campoccia reference teaches away from using the 75% benzyl ester.

Accordingly, Applicants submit that the Examiner's reasoning relies on impermissible hindsight, and accordingly should be reconsidered and withdrawn.

Davidson and Dorigatti

The Examiner rejects claims 3, 5, 13-14, 17-19 and 22 under 35 U.S.C. § 103 as being unpatentable over Davidson in view of Dorigatti (WO 94/17837).

The deficiencies of Davidson have been discussed above.

The Examiner cites Dorigatti for a multi-layer non-woven material comprising esters of hyaluronic acid. However, Dorigatti does not appear to teach a 75% benzyl ester of hyaluronic acid. In particular, on page 4, lines 29-30, Dorigatti discloses that the esters of hyaluronic acid can be used "either singly or in mixtures in varying percentages". However, it is clear from the examples that only the total benzyl ester of hyaluronic acid was made, and that combinations of ester types (*i.e.*, HYAFF 11 and ALAFF 22 in Example 6) were used, but no partial benzyl esters of hyaluronic acid are taught either explicitly or implicitly.

Furthermore, combining Davidson with Dorigatti, one of skill in the art would still lack the 75% benzyl ester of hyaluronic acid because Davidson teaches ethyl esters.

Moreover, one of skill in the art would have no reasonable expectation of success that the 75% benzyl ester could be used to treat scarring, because Dorigatti mentions only that the non-woven tissues of the genera of hyaluronic acid derivatives *might* be used for dermatology (among other purposes), and Davidson does not teach the benzyl ester at all. (Dorigatti, page 3, line 22).

Similarly, Dorigatti makes no distinction between the benzyl esters and the ethyl esters, and thus, one of skill in the art would expect that the benzyl ester would have no effect on scarring, as shown with the ethyl esters of Davidson. Thus, not only would one of skill in the art have no reasonable expectation of success, but one of skill in the art would find the present invention's effectiveness to be unexpected, as described above.

For these additional reasons, Applicants request that the rejection be withdrawn.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of \$1,110.00 is attached hereto.

If the Examiner has any questions concerning this application, the Examiner is requested to contact Leonard R. Svensson, Reg. No. 30,330 at the telephone number of (858) 792-8855. Facsimile communications may be sent to Leonard R. Svensson at the facsimile number of (858) 792-3785.

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Respectfully submitted,

By 

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Attachment: Campoccia Reference
Callegaro Declaration